I, Janet Crook, citizen of the United Kingdom, c/o B.A. Yorke Co., Coomb House, 7 St. John's Road, Isleworth, Middlesex, TW7 6NH, do solemnly declare as follows:

That I am acquainted with the English and French languages, and that the text on the following pages is a true and correct translation of the accompanying Belgian Patent No. 895.724.

And I make this solemn declaration conscientiously believing the same to be true.

Date: 3.7.95 Signature: J. Crook

KINGDOM OF BELGIUM

F. ENT OF INVENTION

No. 895.724

International classification: A 61 K / C 07 C

Ministry of Economic Affairs

Publication date: 28.07.1983

The Minister of Economic Affairs,

In view of the Law of 24th May 1854 on patents of invention;

In view of the Convention of the Union for the Protection of Industrial Property;

In view of the record drawn up on 28th January 1983 at 11.00 a.m.

at the Industrial Property Service;

DECREES:

Article 1. - A patent of invention for: New therapeutical use of dihydrocyclosporin D

is issued to: the said company: SANDOZ S.A., Lichtstrasse 35, CH-4002 Basle (Switzerland)

electing domicile at Sandoz S.A., chaussée de Haecht 226, 1030 Brussels,

the said company having declared that the patent was the subject matter of a patent application filed in Great Britain on 1st February 1982, no. 8202776

Article 2. - This patent is issued to the company without preliminary examination, at its own risk, without a guarantee of the reality, the novelty or the merit of the invention, or of the correctness of the description, and without detriment to the rights of third parties.

There will remain attached to the present decree one of the duplicate copies of the specification of the invention (description and any drawings) signed by the interested party and filed in support of its application for a patent.

Brussels, 28th July 1983
ON SPECIAL AUTHORITY,
The General Manager

Certified copy as correct

J. DEGAVRE
Assistant Counsellor

R. RAUX

DESCRIPTION

filed in support of an application for a

PATENT OF INVENTION

made by

SANDOZ S.A.

for

New therapeutical use of dihydrocyclosporin D

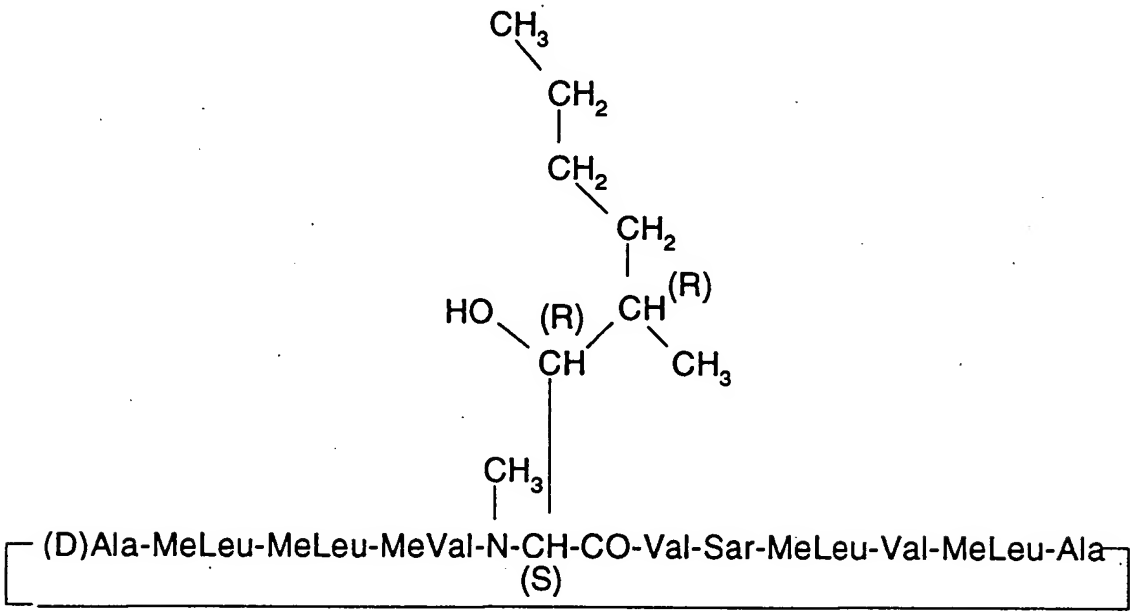
Invention of: Salvatore Cammisuli

Claiming priority of the patent application filed in Great Britain on 1st February 1982 under no. 8202776 in the name of SANDOZ S.A.

Case: 100-5729

The present invention relates to a new therapeutical use of dihydrocyclosporin D.

Dihydrocyclosporin D corresponding to formula



is a known compound. This compound, as well as the process for the production thereof and its use as an anti-arthritic agent, are described for example in U.S. Patent No. 4 220 641, in New Zealand patent application no. 187205, in Australian patent application no. 88764/82 and in Japanese patent application no. 139789/78.

In the course of research, the applicant has now surprisingly found that dihydrocyclosporin D may be used equally well in the treatment of multiple sclerosis, as indicated by the following tests and as may be demonstrated in clinical trials.

1. Action on the experimental allergic encephalomyelitis (EAE) in the rat

EAE is induced in groups of 8 to 12 healthy male rats weighing between 150 and 200 g, in accordance with the method described by Borel et coll. in Agents and Actions 6, p. 468 (1976).

The rats are kept under laboratory conditions with free access to food and water. Onset of EAE is observed after 10 to 13 days, and is marked by symptoms of paralysis, for example of the hind limbs. From the onset of paralysis, food and water is placed close to the animals. Dihydrocyclosporin D is administered orally to the animals at a daily dose of between 25 and 50 mg/kg for 5 consecutive days following the onset of EAE. The rats are examined daily in order to note symptoms of the disease, and the number of recovered rats, as well as the day of recovery, are recorded. Observation is continued for a further 5 to 8 weeks after commencement of treatment with dihydrocyclosporin D, in order to detect any cases of relapse. Again, the number of cases of relapse and the day of relapse are recorded.

Following administration of dihydrocyclosporin D at the dosages mentioned above, a decreased recovery time is observed, compared with the control group to which only olive oil has been administered.

2. Action in preventing the occurrence of EAE in the rat.

The test is carried out in analogous manner to that described above. In this case, however, the compound is administered orally each day at a dosage of between 25 and 50 mg/kg for 14 days starting at the day of sensitisation (induction of EAE). The rats are observed daily for symptoms of paralysis, and the day of onset of EAE in afflected individuals is recorded. Observation is continued for a period of several months in order to detect possible delayed onset of EAE. Following administration of dihydrocyclosporin D at the dosages mentioned above, prevention of the onset of EAE during the observation period is observed, compared with control animals

treated only with olive oil.

Owing to these properties, dihydrocyclosporin D may be employed therapeutically for the treatment of multiple sclerosis. For this application, the dosage to be administered depends on the mode of administration, the condition of the patient and the desired therapy. Satisfactory results are obtained when administering dihydrocyclosporin D in a daily dosage of between ca. 1 and ca. 50 mg/kg, preferably between ca. 5 and ca. 20 mg/kg. The total appropriate daily dosage is between ca. 75 and ca. 3500 mg, preferably between ca. 400 and ca. 1500 mg, advantageously administered in the form of unit dosage forms 2 to 4 times per day, or in sustained release form. The appropriate unit dosage forms for oral administration contain between ca. 15 and ca. 1750 mg, preferably between ca. 100 and ca. 750 mg of dihydrocyclosporin D, in admixture with a pharmaceutically acceptable diluent or solid or liquid carrier.

Suitable galenic formulations for the administration of cyclosporins have been described in the art, for example in German patent application no. 2 907 460.

The invention similarly embraces pharmaceutical compositions which may be used for the treatment of multiple sclerosis, and which contain dihydrocyclosporin D in admixture with pharmaceutically acceptable diluents or carriers.

The following examples of pharmaceutical compositions illustrate the present invention without limiting its scope in any way. All percentages are by weight.

Example 1

Drink solution

Components			Quantity
i)	Dihydrocyclosporin D		5 - 10%
ii)	Absolute ethanol		10 - 12%
iii)	Cremophor® RH 40		ca. 4%
iv)	Maisine®		30 - 40%
v)	Labrafil® 2125	ad	100%

Cremophor® RH 40 is the reaction product of hydrogenated castor oil with ethylene oxide in a molar ratio of ca. 1:40, available from the company BASF AG., Ludwigshafen, Germany.

Maisine® is trans-esterified maize oil, available from Gattefossé, Boulogne-Billancourt, France.

Labrafil® 2125 is a polyoxyethylated kernel oil, available from Gattefossé, Boulogne-Billancourt, France.

The desired quantity of component i) is dissolved according to conventional methods in components ii) to iv), making up a final volume of 100% with v), and the resultant mixture is filled into phials. Before administering, the solution is advantageously mixed with a flavour-masking composition, for example a chocolate-flavoured milk.

Example 2

Soft gelatin capsules

Components		Quantity
i)	Dihydrocyclosporin D	15 - 25%
ii)	Absolute ethanol	2 - 5%
iii)	Imwitor® 742	10 - 40%
iv)	Maisine®	40 - 60%

Imwitor® 742 is a glycerine ester available from the company Dynamite Nobel AG, Troisdorf-Obelar, Sweden.

The quantity of component i) required for a single dose is dissolved in components ii) to iv) according to conventional methods, to give a solution suitable for filling into a soft gelatin capsule.

The invention similarly embraces a medicament for the treatment of multiple sclerosis, which contains dihydrocyclosporin D as the active ingredient.